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Multiple sclerosis management in pregnancy

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Summary

Multiple sclerosis (MS) is the most common chronic neurologic disability in young adults in their childbearing ages of 20 to 45 years. The disease affects especially women that is worthy of discussion among pregnancy-related conditions in a woman with MS. Prenatal counseling to discuss the safety of medications in pregnancy, the antepartum period, along with what the patient can expect during birth, and the postpartum period will be discussed.

Key words: Multiple sclerosis; Pregnancy; Antepartum; Postpartum.

Immunological background of MS

Neuroinflammation is involved in several neurodegenerative disorders including multiple sclerosis (MS) and emerging evidence indicates that it constitutes a critical process that is required for the progression of neurodegeneration. Microglial activation constitutes a central event in neuroinflammation with microglial cells being the main source of reactive oxygen species (ROS) and nitrogen species, glutamate, and TNF-α [1, 2]. MS is a neurodegenerative autoimmune disorder in which axon demyelination lesions develop in the central nervous system and T-cell-mediated response has been known to be involved for more than a decade [3].

MS is characterised by the progressive loss of neurological function caused by the destruction of the axonal myelin sheath in several areas of the brain and the spinal cord, which is mediated, mainly, by self-reactive CD4+ T-cells [4].

The loss of myelin is manifested in clinical symptoms such as: paralysis, muscle spasms, optic neuritis, and neuropathic pain [5]. The pathological features of MS lesions involve: blood-brain barrier (BBB) permeability, myelin sheath destruction, axonal damage, glial scar formation, and presence of inflammatory cells infiltrated into the CNS [6].

Experimental model of MS

The most used and accepted animal model equivalent of MS is experimental autoimmune encephalomyelitis (EAE), which corresponds to an induced autoimmunity in mice [7]. The administration of myelin-derived antigens in an immunogenic context induces the activation of self-reactive T-cells that are specific for myelin antigens, mediating myelin destruction. This induced autoimmunity is characterised by focal areas of demyelination along the brain and spinal cord, with axonal loss that results in ascending paralysis, affecting first the tail and then the hind limbs [8]. This initial neuroinflammatory process results in BBB disruption and the entrance of leukocytes into the CNS parenchyma. Once T-cells enter the CNS, they are re-stimulated by resident antigen-presenting cells (APCs), such as astrocytes, microglia or infiltrated APCs such as dendritic cells and macrophages [9].

Th17: main culprit in MS

The experimental autoimmune EAE model of MS provided the first clues to the possibility that other T cell effector functions, beyond those attributed to the Th1 and Th2 subsets, could be contributing to the onset and progression of MS [10]. Researchers have further explored the link between autoimmunity and environmental factors by looking at the effect of a high salt diet, such as is seen in a typical "Western diet", in the pathology of autoimmunity, specifically Th17 cells [11]. Vitamin D can act as another source of Th17 regulation, as the vitamin D receptor is induced in Th17 cells [12]. A metabolite of vitamin A, retinoic acid, has also come into the spotlight as a potent attenuator of immune function and has been shown to have effects on T cell differentiation and function [13]. Human blood-brain barrier endothelial cells were found to express receptors for IL-17 and IL-22, thus making it possible for IL-17 and IL-22 to disrupt blood brain barrier junctions [14]. It was also found that human Th17 lymphocytes were able to migrate past blood-brain barrier-associated cells, where they continued to promote inflammation through CD4+ T cell recruitment and inflammatory cytokine production [14]. With regards to the role of microbiota in the prevention or progression of EAE and MS, reports have thus far been varied. Researchers have shown that the use of specific probiotic mixtures is able to suppress EAE development though Th1/Th17 polarization inhibition, and increases

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Foxp3+ Treg numbers and IL10 production [15]. Yokote *et al.* also demonstrated that the administration of antibiotics altered gut flora composition and ameliorated EAE development through a possible invariant natural killer cell-Th17 interaction-dependent mechanism [16].

MS symptoms

MS is caused by an autoimmune response involving macrophages and cytotoxic T cells that cause a chronic inflammatory state resulting in damage to the myelin sheath around nerve cells. The demyelination of axons causes both acute and chronic lesions to develop in the central nervous system altering the conduction of electrical impulses to muscle groups. Varying MS symptoms occur based on the location of lesions such as pain, bowel and bladder dysfunction, seizures, sexual dysfunction, discoordination-tremor, vertigo, and sensory changes. Moreover vision, speech, muscle strength, and sensation are commonly affected by MS. Physical symptoms can be accompanied by memory loss, cognitive impairment, depression, mood swings, and fatigue [17, 18]. Infection, stress, pregnancy, postpartum period, fatigue, heat, and heavy metal exposure may cause exacerbation of MS symptoms [19].

Diagnosis

Although onset of MS is uncommon during pregnancy, women's healthcare providers require an understanding of diagnostic criteria to better discuss prognosis and pregnancy-related concerns. In addition to clinical symptoms and physical examination finding (Lhermitte's sign, dysesthesias, Tic douloureux), the diagnosis includes evidence of MRI lesions in at least two places in the central nervous system, at least one month apart, and differential diagnoses are ruled out. Over half of MS women had MRI changes in the last trimester of pregnancy and within four to 12 weeks of postpartum. An increase in new or enlarging MRI lesions postpartum was reported in several studies [20]. Differential diagnoses include migraine, cerebral neoplasms, nutritional deficiencies of vitamin B12 or copper, compressive lesions of the spinal cord, human immunodeficiency virus, syphilis, lupus, or psychiatric disease.

MS in pregnancy

Prenatal counseling

MS is believed to be caused by a combination of several factors including immunologic, genetic, and environmental factors. Previously, pregnancy was discouraged in women with MS; however, recent studies have shown pregnancy as potentially having a beneficial role on MS relapse rates with no effects to long-term progression of the disease [21, 22]. Babies of mothers with MS have a higher risk (4%) of developing the disease compared with the general population (0.1%) [23]. If both parents are affected by the disease, the risk for offspring increases to 30.5% [24]. Currently, there are no prenatal diagnostic tests that predict MS.

Antenatal care in MS

Preterm labor rates are not higher in women with MS; if MS woman have impaired sensation she may not perceive preterm contractions or pelvic pressure [25, 26]. If preterm labor requires tocolysis, calcium channel blockers should be used. Caution is used with administration of magnesium sulfate, which causes fatigue and weakness. When strict bed rest is prescribed, venous thromboembolism prophylaxis is recommended until the woman is able to ambulate.Women with MS have increased risk of urinary tract infection during pregnancy that may cause exacerbation of the woman's MS symptoms. Recommended routine monitoring for urinary tract infection and chronic antibiotic prophylaxis may be appropriate [26].

Medical therapy of pregnant women with MS

Pregnancy appears to have no influence on the progression of disability in MS. Confavreux *et al.* reported that the frequency of relapses, decreased by 80% up to the third trimester, increased in the immediate postpartum period, and returned to pre-pregnancy levels at six months [27]. Eight therapies are currently approved for treatment of MS: glatiramer acetate (GA), subcutaneous interferon b (IFNb)-1a, intramuscular IFNb-1a, subcutaneous IFNb-1b, fingolimod, natalizumab, teriflunomide, and mitoxantrone. Based on current literature data, IFN-β and glatiramer acetate (GA) appear to be most suitable for use up until the time of confirmed pregnancy. They are not associated with teratogenic risk or a higher risk of miscarriage. Relapses during pregnancy can be treated with corticosteroids but caution is advised prior to gestational week 12 because of the risk of cleft palate. In the case of severe relapse in the first trimester, the preferred treatment is prednisolone as it is inactivated in the placenta, because only about 10% reaches the fetus versus 100% with dexamethasone. In women receiving continuous corticosteroid therapy, premature rupture of the membranes can occur. Natalizumab is unlikely to cross the placental barrier to any great extent during early pregnancy. Therefore natalizumab should be discontinued at a maximum of three months prior to pregnancy. If natalizumab is administered in the third trimester of pregnancy, some haematological abnormalities such as thrombocytopenia and anaemia may occur. Effective contraception is advised for at least two months after cessation of fingolimod treatment and breastfeeding is contraindicated. Teriflunomide has teratogenic effect in animal studies. Therefore pregnant women have teriflunomide exposure during pregnancy should be using cholestyramine or activated charcoal. Alemtuzumab use in pregnancy has no harmful effect with respect to obstetrical and fetal outcomes. For MS patients with aggressive disease, treatments include immunosuppression or chemotherapy, followed by autologous

stem cell transplant [20]. Mitoxantroneis, a cytotoxic chemotherapeutic agent is used for secondary progressive MS. Use of mitoxantrone during pregnancy has shown teratogenic effects in the developing fetus and intrauterine growth restriction at low doses in rats.

Breastfeeding in MS

Recent meta-analysis reported that association between breastfeeding and MS relapse showed a tendency for fewer relapses in women who breastfed, suggesting that exclusive breastfeeding may reduce early postpartum relapses [28]. Furthermore, breastfeeding appears to be safe while patients receive IFN-β and GA, natalizumab, and other non-depleting monoclonal antibodies, but not small molecules such as fingolimod and dimethyl fumarate.

Obstetrical outcome in MS

Pregnant women have high levels of circulating lymphocytes and macrophages and decreased production of proinflammatory cytokines. These immune system changes appear to have a cumulative, beneficial effect on MS by decreasing the incidence of a first clinical demyelinating event. In addition, there is evidence that with each additional pregnancy that the incidence continues to decrease. The frequency of relapse during pregnancy drops, with the third trimester being the lowest. However, for three to six months after delivery, the relapse rate significantly increases [29, 30]. With regards to obstetrical outcomes, the course of pregnancy is similar to that of women without MS but with a tendency towards assisted delivery/cesarean section and possibly lower neonatal birth weights. One study reported that women who received epidural anesthesia of bupivacaine had a higher incidence of postpartum relapses [31]. However, other studies failed to demonstrate any evidence of an increase in postpartum relapse rate, based on the mode of obstetrical anesthesia [32]. But another study conducted in women with MS were found to have a higher incidence of labor induction, longer second stage of labor, more operative vaginal births, and cesarean deliveries, and their infants had lower birth weights [33]. However, neonatal mortality rates were not increased. Reported most recently was a 30% higher risk for cesarean birth and a 70% increase of intrauterine growth restriction, as compared to healthy women [34]. MS has no any effect for miscarriage or congenital malformation [32].

Oral contraceptives (OCs) use and other hormonal treatment in MS

The estrogenic and progestagenic influence of oral contraceptive use increase the prevalence of MS. Another study suggests that estrogen may have protective effects against disease progression and have no adverse effects of incidence, overall prognosis, or disability severity in women with MS [35, 36]. The results of a well-matched case-control study adjusted for MS risk factors showed an increased risk of MS with use of combined OCs [35]. Short-term methylprednisolone therapy does not appear to have an adverse effect on fertility, whereas menstrual disturbances have been reported with interferon beta and permanent amenorrhea with mitoxantrone, especially in women older than 35 years [37].

Infertility treatment in MS

In general, fertility does not seem to be reduced in women with MS. However, infertility and MS might just occur coincidentally due to a higher incidence of hyperprolactinemia, thyroid disorders and endometriosis [37], higher levels of prolactin, follicle-stimulating hormone, luteinizing hormone, total and free testosterone, 5-α dihydrotestosterone, δ-4 androstenedione levels, and decreased levels of estrone sulfate [38]. Men with MS may have impaired fertility due to decreased sperm count, mobility, and normal sperm development [39]. Therefore, MS patients might undergo assisted reproductive treatment (ART).

Studies reported an increase in annualized relapse rate after ART, particularly in the first three months after unsuccessful cycles [37, 40]. Recent study reported that infertile women with MS who underwent IVF showed a seven-fold increase in the risk of MS exacerbation and a nine-fold increase in the risk of disease progression with new brain lesions [41]. The risk appears to be greater with use of GnRH agonists cycles. Putative mechanisms involved in MS worsening after ART include: temporary interruption of disease modified therapies, stressful events associated with IVF treatment, and immunological changes induced by cytokines and hormones, such as increase in pro-inflammatory cytokines, estrogens, and progesterones, as well as an increase in immune cell migration across the blood-brain-barrier. Overall, obstetricians and neurologists should be aware of this risk and discuss the pros and cons of the procedures with MS patients [42]. MS patients requiring ART should be stabilized before patients undergo the IFV procedure.

Conclusion

Although onset of MS in pregnancy is uncommon, large numbers of female patients express desire to become pregnant after receiving MS diagnosis. Therefore, issues of contraception, conception, pregnancy, childbirth, and child rearing become critically important in the overall management strategies of MS patients and have been of great interest to neurologists, obstetricians, and reproductive specialists. It is known that the risk of MS relapse declines during pregnancy but increases in the first three to six months postpartum. It is also known that this risk is not affected by delivery method, anesthesia type, or parity. IFN-β and glatiramer acetate appear to be most suitable for use up until the time of confirmed pregnancy. Decision regarding the mode of delivery is usually based on obstetrical rather than neurological factors. Infertile women with MS who underwent IVF showed a seven-fold increase in the risk of MS exacer-

bation and a nine-fold increase in the risk of disease progression with new brain lesions. The hormonal influence of oral contraceptive use increase the prevalence of MS.

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